California Medicine

A REVIEW

Practical Aspects of GENETICS *for Physicians*

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THE INCREASING NUMBER of articles concerned with medical genetics attests the growing significance of this subject to medicine. Many of the recent advances in genetic knowledge can be applied to the practice of medicine. In this brief review it has been necessary to be selective in the choice of material covered; emphasis has been placed on those aspects which will help practicing physicians toward a better understanding of the role of genetics in relation to disease.

After a discussion of basic concepts, the following topics will be considered: types of inheritance; population genetics; cytogenetics; dermatoglyphics; pharmacogenetics; heterozygote detection; genetics as an aid in diagnosis; immunogenetics; mental diseases; genetics and radiation; treatment and management of genetic diseases; genetic counseling; consanguinity; and sources of genetic counseling in California.

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Basic Concepts[33,34]

Heredity and Environment. An important problem in medical genetics is to define the role and importance of heredity in a disease. A useful model for visualizing this relationship is to consider disease as the result of interaction between environmental and host factors. Host factors are to a large degree genetically determined or influenced. Therefore, variability in individual responses to the same environmental stress may be attributed to hereditary factors. The genetic constitution of an individual plays some role in all diseases, since it determines the potential or limits of the body's ability to respond to environmental factors. For example, in a traumatic fracture, the inherent make-up of the individual influences the bone structure so that it may break under stress. Thus, the genetic constitution is a necessary, but frequently not a sufficient cause for a disease to occur.

Much of current genetic knowledge of normal people has come from the study of single gene-

determined diseases. These diseases offer specific, and well-defined variations from the normal, and as such offer good material for the study of inherited variations.

The Gene: Definition in biochemical and Mendelian terms. Genes are considered to be the basic units of heredity; one gene controls the formation of one polypeptide chain with structural or enzymatic functions. The information necessary to specify the sequence of amino acids in the polypeptide chain is contained in the nucleotides of the deoxyribonucleic acid (DNA) within the cell nucleus. This information is transmitted from the nucleus by a special type of ribonucleic acid (RNA) to the cytoplasm where the specific polypeptide chains are formed.

There are two types of cell division. *Meiosis* describes division which occurs only in the germ cells. The mature sperm or egg is *haploid,* containing 23 or only half the usual number of chromosomes as compared with the *diploid* number of 46 found in other cells of the human body. In the non-germ or somatic cells, cell division occurs through *mitosis,* in which the daughter cells have the same number of chromosomes as the mother cells and an identical genetic composition.

Almost one hundred years ago Mendel first noted that inherited characteristics seem to function as discrete units, and retain their individuality from generation to generation. This concept of genetic transmission and *segregation* has been succinctly stated by Ford[6]: "The genes are present in pairs (*allelomorphs*) as are the chromosomes (*homologous chromosomes*). The members of these pairs, both of genes and of chromosomes, are derived respectively from the two parents. Consequent upon Mendelian *segregation,* the genes constituting the allelomorphs separate from one another and pass into different gametes, as do the members of the homologous pairs of chromosomes, owing to meiosis. The gametes then contain one member only of the pairs, both of genes and chromosomes; but these are restored by the additive nature of fertilization." Mendel also described the *law of independent assortment.* When two or more pairs of genes segregate during meiotic cell division, distribution of any one of them is independent of the distribution of the others, unless the pairs are linked—that is, located on the same chromosome.

Structural and Regulatory Genes. Recent work in microorganisms suggests that there are two types of genes. One is a *structural gene* which determines the amino acid sequence of a polypeptide chain and the other which determines the time that a structural gene will form its product.[22] This latter has been referred to as a *regulatory gene* and although definite proof for its existence in man is incomplete, thalassemia is a possible example. In this hereditary blood disorder the production of normal polypeptide chains in part of the hemoglobin molecule is reduced. This is in contrast to other hemoglobinopathic conditions, such as sickle cell disease, in which an abnormal polypeptide chain is formed.

Mutations. A mutation is a change in the genetic material which is transmitted to future generations of cells and in which the mutant gene forms a product different from normal. Gene mutations can occur in either the somatic or the germ cells. Those in somatic cells are not transmitted to children; germ cell mutants can be transmitted to children. It is generally believed that the majority of mutations are detrimental, as might be expected, since a random change or mutation in a well-ordered and balanced mechanism is more likely to be harmful than beneficial. The effect of radiation on mutation will be discussed later.

Penetrance and Expressivity. Variation in the manifestations of a given gene in different individuals is recognized. Two terms frequently used in describing this phenomenon are *expressivity* and *penetrance.* Although often used interchangeably, they have different genetic meanings. *Expressivity* refers to the differences in degree or severity of manifestations, and *penetrance* is a statistical term referring to manifestation rate; for example, if 100 people carry a gene and 50 people show manifestations of it, there is 50 per cent penetrance.

Other Genetic Terms. Genotype refers to the genetic composition of an individual. *Phenotype* refers to the manifestations of a gene ranging from the initial gene product to the gross anatomical anomalies seen in some clinical diseases. A *phenocopy* is an environmentally determined phenotype similar to a genetically induced phenotype, whereas, *genocopy* refers to a phenotype produced by a gene different from the gene usually determining the phenotype.

A pair of genes (allelomorphs or *alleles*) on a pair of homologous chromosomes determine a specific hereditary trait. If the *allelic* genes are different, the individual is *heterozygous;* if they are the same, he is *homozygous.*

Types of Inheritance[6,33]

Autosomal dominant, autosomal recessive, and *sex-linked* are terms which refer to the patterns of transmission and the manifestations of the genes, and not to the genes themselves. Table 1 lists the characteristics of these patterns of inheritance.

In man there are 23 pairs of chromosomes; 22 pairs are autosomes and the remaining pair are the sex chromosomes. The female has two X chromo-

somes; the male has one X and one Y chromosome. A large number of genes on the X chromosome have been identified, but the Y chromosome appears to be relatively deficient in genes, its importance seemingly related to the formation of testes.

The *Lyon hypothesis* has been advanced to explain the activity of genes on the X chromosome.[16] The main clinical importance of this theory is that it accounts for manifestations of sex-linked traits in some female carriers. A *sex chromatin body (Barr body)* is found in the nucleus of somatic cells of the normal female with two X chromosomes, but is absent in the male with one X chromosome. The Lyon hypothesis proposes: (1) the sex chromatin body represents an X chromosome which is genetically inactive; (2) the inactivation of the X chromosome occurs early in the life of the embryo; (3) either X chromosome from the mother or from the father can be inactivated in a random fashion; and (4) all cells derived from a cell with a given inactivated X chromosome will have the same X chromosome inactivated. Some expected and observed consequences of this hypothesis are: (1) a normal female is a mosaic in whom some cells have one X chromosome active and the other cells have the other X chromosome active; (2) females as a group should show wide variability for traits controlled by genes on the X chromosome, so that some female carriers may actually manifest a sex-linked trait, such as muscular dystrophy or hemophilia; and (3) female identical twins should show greater intrapair differences than identical male twins.

This section on inheritance patterns will be completed with a few words about the family pedigree, which is a short-hand way of recording the family history.[3,33] Once the system and symbols become familiar, this method offers advantages over the usual verbal description of the family history. It is much easier to recognize inheritance patterns, to see at a glance the relation of the various family members to one another, and in general to make a more useful and meaningful record.

Population Genetics[33]

In addition to the study of gene manifestations in individuals and inheritance patterns in families, geneticists are interested in the frequency of genes in a population and how these may contribute to its characteristics. The basic principle dealing with population genetics is known as the Hardy-Weinberg law, which serves to illustrate how gene distributions can be estimated in a population. For illustration, it will be assumed that "A" and "a" represent two allelic genes. Since allelic genes occur in pairs the following pairs are possible: AA, Aa, and aa. The problem is to determine their relative frequencies. The law can be condensed into a binomial formula: $p^2 + 2pq + q^2 = 1$, and $p + q = 1$; by letting the frequency of gene "A" $= p$ and that of gene "a" $= q$, then AA $= p^2$, Aa $= 2pq$ and aa $= q^2$. By use of this formula, the frequencies (as noted in Table 2) can be estimated. For example, if a recessive disease, such as phenylketonuria, has a frequency of 1:10,000, then one person in 51 is a carrier of the mutant gene. Based on the present estimated population of 180,000,000, there would be about 3,530,000 persons who are carriers of this gene in the United States. Although a recessive disease may be rare, a large number of the population will carry the gene in the heterozygous state.

Cytogenetics[9,11,12]

It has been nine years since the chromosome number in man was found to be 46, and five years since the first known anomaly was demonstrated in man. Subsequently several chromosomal abnormalities have been found in association with clinical syndromes.

Familiarity with Figure 1 will help to make the following discussion more meaningful. This picture shows the metaphase chromosomes of a normal man arranged in an arbitrary pattern known as a karyotype. The chromosomes occur as homologous pairs, except in the male, where the sex chromosomes, X and Y, are not homologous. The chromosome pairs are numbered from 1 to 22 in decreasing size. The arrangement is also based on the constant position of the *centromere*, the point where the two *chromatid arms* of the chromosome are joined. The chromosome pairs are also organized into groups from A to G, since it is not always possible to distinguish definitively between the chromosome pairs in a given group.

The chromosomes have differing appearances during the life cycle of the cell. They are best visualized at *metaphase* or just before the cell divides. In the presence of colchicine, cell division is stopped at metaphase and a number of cells in mitosis can be accumulated for study. These chromosomes can be photographed and the individual chromosomes cut from the print and arranged into a karyotype as seen in Figure 1.

Chromosome abnormalities involve both the autosomes and the sex chromosomes, and include variations in their number and structure. Some of the more common anomalies will be briefly discussed.

The term *trisomy* is used to denote the presence of three similar chromosomes rather than a pair. For example, trisomy 21 indicates that there are three No. 21 chromosomes rather than two. This finding is common in mongolism or Down's syndrome. Two other well-recognized trisomies each

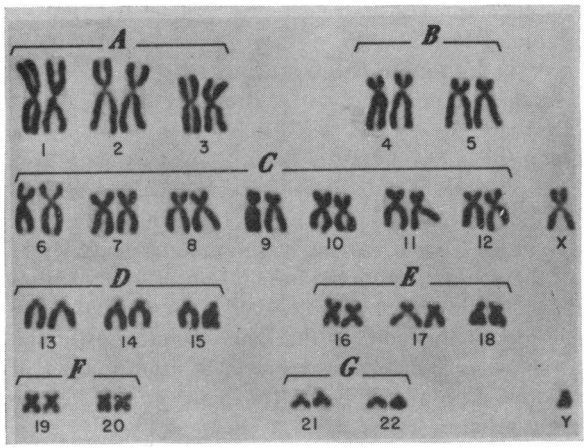

Figure 1.—Karyotype of metaphase chromosomes from a normal human male.[1]

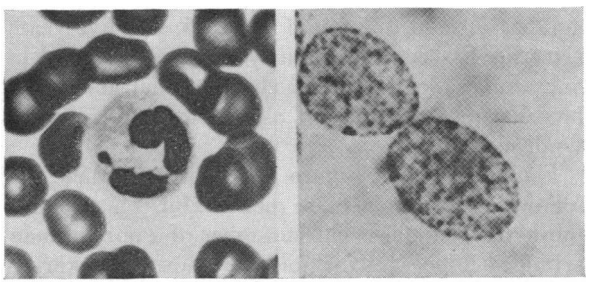

Figure 2.—The polymorphonuclear neutrophil on the left demonstrates the nuclear appendage, known as the "drumstick," projecting to the left of the lower lobe of the neutrophil. On the right are two somatic cell nuclei, each having a single sex chromatin body at the periphery of the nucleus; this dark appearing body is at the bottom of the nucleus on the left and on the top of the nucleus on the right.

involve a chromosome pair in the D and in the E group, and are called D_1 (13-15)' and E (17-18) trisomies or syndromes. Because of the difficulty in assigning the trisomy to a particular chromosome pair, the group designations D and E often are used. *Monosomy*, the presence of only one member of a chromosome pair, has not been described in the autosomes, suggesting it may be lethal.

Deficiencies as well as excess numbers of the sex chromosomes have been found. *Monosomy* for an X chromosome, XO, is a frequent finding in the Turner syndrome. A YO individual has not been described, since such a chromosome constitution would probably be lethal. The presence of extra Y chromosomes (for example, XXY) seems to have relatively little effect, whereas extra X chromosomes in the presence of a Y chromosome (for example, XXY, XXXY) leads to the Klinefelter syndrome. In the female, extra X chromosomes (for example, XXX or triple-X syndrome) seem to have no consistent well-defined effect.

Numerical changes in chromosomes arise from errors during division of the cell and distribution of the chromosomes to the daughter cells during mitosis or meiosis. Two types of errors have been described: *anaphase lag* in which a chromosome does not move in the normal manner to one or the other daughter cell; and *nondisjunction* in which chromosomes that normally separate move together to the same daughter cell, causing one cell to have an extra chromosome and the other to lack this chromosome.

An example of a structural change is a deleted chromosome in which some chromosomal material is lacking. A well-described deleted chromosome is the *Philadelphia chromosome (Ph¹)* which is found only in the blood and the bone marrow cells of patients with chronic myelogenous leukemia.[20] The involved chromosome is thought to be one member of pair 21, the same pair which is affected in mongolism. Such an individual is a *mosaic* because some cells have a normal karyotype and other cells have the deletion karyotype. Other types of mosaicism have also been recognized; for example, some individuals with mongolism have been found to have some cells with a normal karyotype and others with the trisomy 21 karyotype.

Another structural abnormality is a translocation in which there is a transfer of chromosomal mate-

TABLE 1.—*Characteristics of Inheritance Patterns*

I. AUTOSOMAL DOMINANT
1. Gene is located on one of the autosomes.
2. Gene is present in the heterozygous state.
3. Trait is found in successive generations.
4. About 50 per cent of the children of an affected parent can be expected to also be affected.
5. Males and females are equally affected.

II. AUTOSOMAL RECESSIVE
1. Gene is located on one of the autosomes.
2. Gene is present in the homozygous state.
3. Tends to be limited to one generation with one or more siblings affected.
4. Each of the parents of an affected individual is a heterozygous carrier of the mutant gene and generally shows no manifestation of the gene.
5. In many of the rare traits there is an increase in consanguinity or marriage between blood relatives in the parents of the affected individual.
6. A mating between heterozygote carriers produces on the average: 25 per cent of the offspring are homozygous for the gene, 50 per cent are carriers, and 25 per cent will not have the gene.
7. Males and females are equally affected.

III. SEX-LINKED (X-linked)
1. The gene is located on the X chromosome.
2. The trait is usually limited to males.
3. Females carry but usually do not show manifestations of the gene.
4. The trait tends to skip generations since affected males have asymptomatic carrier daughters who in turn transmit the gene to half their sons.
5. Affected males may have affected male relatives on the maternal side of the family.
6. There is never transmission from father to son, because the son receives the Y and not the X chromosome from the father.

rial from one chromosome to another. In humans this has been described only for the autosomes, although it probably also involves sex chromosomes at times.

As mentioned earlier in the discussion of sex-linked inheritance, sex chromatin or Barr bodies are found in the somatic cell nuclei of humans with two or more X chromosomes. These are currently believed to represent inactive X chromosomes. The maximum number of such bodies for a cell is one less than the number of X chromosomes, irrespective of the presence of a Y chromosome (see Table 3). Therefore, examination of cells for this structure when a sex chromosome abnormality is suspected may be helpful and certainly is easier and much less time-consuming than a chromosome analysis. Figure 2 shows the appearance of a sex chromatin body in a somatic cell nucleus. Polymorphonuclear neutrophils in females sometime have a drumstick (see Figure 2) or small nuclear appendage and this is generally considered to be the manifestation of the sex chromatin body for this type of cell.

Dermatoglyphics[25,35]

Dermatoglyphics or the study of finger, palm and sole prints has recently received renewed attention because alterations from normal in these patterns have been found in persons with certain chromosome anomalies. The pattern of fingerprints is to a large extent genetically determined, is established in the first four months of embryonic life and does not change thereafter. Possibly because several genes are involved in determining a pattern, fingerprints are unique for each individual and are useful for purposes of identification. They have also been found useful in determining whether twins are monozygous (identical) or dizygous (fraternal or nonidentical), an important fact if twins are to be used in genetic studies.

TABLE 2.—*Gene Frequencies Based on the Hardy-Weinberg Law for Simple Single Factor Recessive Inheritance*[33]

Frequency of Affected Homozygotes (q^2)	*Frequency of Heterozygote Carriers ($2pq$)*
1 in 10	1 in 2.3
1 in 100	1 in 5.6
1 in 1,000	1 in 16
1 in 10,000	1 in 51
1 in 100,000	1 in 159
1 in 1,000,000	1 in 501

TABLE 3.—*Quantitative Relation of Sex Chromatin Bodies to the X Chromosomes*

Number of Sex Chromatin Bodies	*Sex Chromosome Constitution*	
	Male	*Female*
0	XY, XYY	XO
1	XXY, XXYY	XX
2	XXXY	XXX
3	XXXXY	XXXX

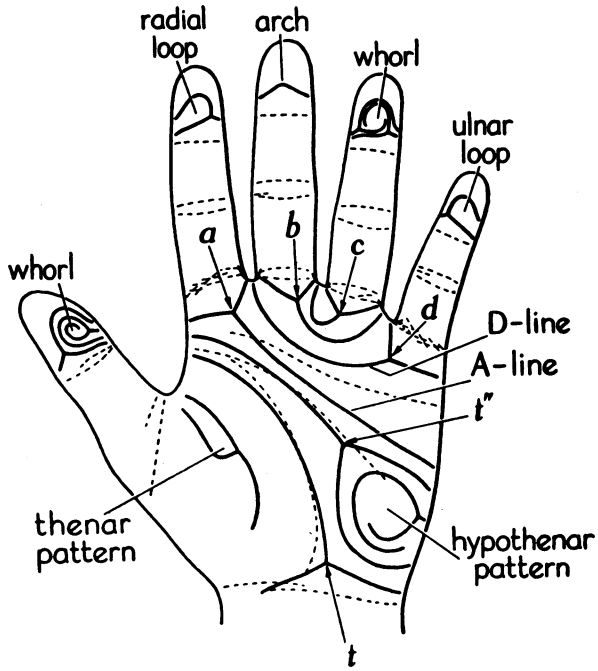

Figure 3.—Diagrammatic patterns formed on the palm and finger tips by the fine lines and ridges (not the creases). Triradii are formed when three ridges intersect: t represents the normal position and t" an abnormal high or raised palmar triradius; a, b, c, and d are also triradii; and, as demonstrated by the finger tip patterns, an arch has no triradius, a loop has one and a whorl has two triradii.[25]

Figure 3 shows diagrammatically some dermatoglyphic patterns and the terms used to describe these findings. The patterns correspond to the dermal ridges and not the obvious flexion creases. The finger tip patterns are the best known and most extensively studied.

Although the dermatoglyphic patterns are not pathognomonic, study of them can often be useful or confirmatory in a suspected diagnosis. The patterns can usually be recognized with the naked eye or with the help of a magnifying glass. For accurate analysis a print is necessary. It is difficult to make prints of the fingers of young infants and their patterns tend to be less distinct.

The following are brief descriptions of the findings in some of the chromosome anomalies. The most extensively studied disorder is mongolism (Down's syndrome). The characteristic findings in mongolism are: high palmar triradius (t" in Figure 3) which normally is less than a third of the distance from the distal wrist fold to the proximal crease of the middle finger; increased ulnar loops on the fingers (that is, the loops open to the ulnar side of the hand); and the presence of a loop

pattern in the third interdigital area (between triradii *b* and *c* in Figure 3). When the distal transverse palmar crease runs completely across the palm, it is known as a simian line or crease. Such a crease is common in mongolism.

In the E trisomy (17-18) syndrome there is an increased number of arches in the finger tip patterns.

Persons with the D_1 trisomy (13-15) syndrome frequently have a high palmar triradius and a simian line, both of which are also found in mongolism.

A quantitative analysis has been developed by Walker[36] for the dermatoglyphic analysis of the prints in mongolism. (For those who are interested, the details are best read in the original reference.)

Pharmacogenetics[5,19]

Pharmacogenetics is the study of genetically determined variations that are revealed by the effects of drugs. The metabolism of drugs by the body is through enzymes which are genetically determined. Absorption, plasma-binding, interaction between drug and cell, breakdown, conjugation and excretion may be affected by enzyme action. At any of these levels minor genetically determined enzyme variations may occur. These variations, in association with environmental effects, combine to give a unimodal or normal distribution curve for drug decay or pharmacologic response. However, a bimodal or trimodal distribution suggests a single major gene effect. A number of genetically determined pharmacologic responses have been found in man.

Persons treated with INH (isoniazid) have been classed as slow or rapid inactivators of this drug. This characteristic appears to be determined by a single major gene concerned with the acetylation or inactivation of INH. The persons who are slow inactivators are homozygous for a mutant gene and constitute about half the American white population. A practical consequence of this phenomenon is that INH-induced polyneuropathy is almost limited to the slow inactivators who have high blood levels of INH.

About one person in three thousand may experience prolonged apnea when exposed to the drug suxamethonium, a muscle relaxant commonly used in anesthesiology and electroshock therapy. Affected persons are homozygous for a mutant gene which produces an atypical pseudocholinesterase. Apnea results because this atypical enzyme inactivates suxamethonium at a reduced rate, thereby permitting the drug to act longer than normally.

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is a well-studied X-linked enzyme defect affecting the first part of the oxidative pathway of carbohydrate metabolism. This defect was first noted in Negroes who had hemolytic reactions when treated with the antimalarial drug primaquine. Subsequently many drugs (for example, sulfa drugs and nitrofuran derivatives) have been found to cause this reaction. Affected Caucasians also have been described and they tend to have a more severe enzyme deficiency than do Negroes. Favism, hemolysis during infection, certain types of nonspherocytic hemolytic anemia and some cases of neonatal jaundice have been attributed to this enzyme defect. Since about 11 per cent of American Negro males have the trait, it becomes a practical consideration in unexplained hemolytic anemia in this group.

A decided variability in the response to certain coumarin drugs has been recognized for years, but only recently has there been described a specific hereditary transmission of exceptional resistance to coumarin anticoagulants. This represents the first example of hereditary drug resistance in man.[21]

Drugs are useful in the detection of asymptomatic heterozygote carriers of disease; for example, the increased urinary excretion of pentose in carriers of the gene for pentosuria in response to the administration of glucuronolactone, or in defective salicylate conjugation in carriers of the Crigler-Najjar syndrome. In some situations drugs will precipitate a disease—barbiturates touching off acute intermittent porphyria, for example, and possibly the production of a Parkinson-like syndrome by phenothiazine in certain individuals.

Heterozygote Detection[13,18,37]

Knowing that a person is a heterozygote carrier may have little direct application to the health of the carrier himself, but it might play a significant role in the health of his children should he marry someone heterozygous for the same recessive trait. Table 4 indicates a number of disorders in which the carrier state may be identified; however, not all of the females heterozygous for an X-linked gene can be identified.

Genetics as an Aid in Diagnosis

Genetic research has led to the separation of groups of diseases with similar clinical pictures into individual distinct diseases. For example, six different syndromes involving intestinal polyps have been described.[14] These are: (1) familial polyposis of the colon, an autosomal dominant disease with strong malignant tendencies; (2) the similarly inherited distinct polyps of the rectum and colon with malignant potential; (3) the autosomal dominant Peutz-Jeghers syndrome in which benign polyps of the gastrointestinal tract are associated with pigmentation of the buccal mucosa, lips and fingers;

(4) the Gardner syndrome in which premalignant polyps of the colon occur with soft tissue tumors and osteomata; (5) the rare Turcat syndrome of polyposis with a tumor of the central nervous system; and (6) the rare association of polyps with multiple endocrine adenoma.

External signs in genetic disorders may lead to recognition of internal disease—for example, the Peutz-Jeghers syndrome and the Osler-Rendu-Weber syndrome (hereditary telangiectasia). Some diseases, such as the Hurler syndrome, may be due to different genes, the effects of which are clinically indistinguishable. One form is X-linked and the other is an autosomal recessive trait. Although the sex-linked variety tends to be a less severe disease, both types are grave illnesses and the main advantage in distinguishing the syndromes is that accurate genetic counseling can be given for other family members. At present the best way to distinguish the two diseases is through a careful family history to establish the pattern of inheritance.

Immunogenetics[27]

Both the immunologic and genetic aspects of the blood groups have been thoroughly studied. This knowledge has formed the basis for blood transfusion therapy and is a major step toward the understanding of erythroblastosis. The blood groups are under genetic control, each type being determined by a single gene. For each given blood group system, such as the ABO or MN, a specific and separate genetic locus is involved. Recently the first X-linked blood group, Xg^a, was discovered.[16]

Considerable attention has been focused on the immunogenetics of tissue transplantation.[4] At least several genetic loci are involved in determining the antigens of tissue cells. All or almost all of these genetically determined antigens must be alike in two individuals—for example, as in identical twins —if a successful tissue transplant is to be expected. The problem of typing tissue cells in a manner similar to that used for the blood cell types, is under investigation in the hope that selection of a donor antigenically similar to a recipient can be determined before a transplant is attempted. Another approach to the transplantation immunity problem is the use of radiation or drugs to suppress the immunological competence of the recipient so that he will not reject a tissue graft, even if it contains foreign antigens. Success in these endeavors will make possible a host of therapeutic measures not currently available.

Mental Diseases[24]

The genetic aspects of mental retardation and psychiatric illness present unresolved problems. Some instances of mental retardation can be explained on a simple genetic basis. These include metabolic defects such as phenylketonuria and galactosemia, and chromosome anomalies such as mongolism. However, the majority of mental disorders have no explanation in terms of a recognized environmental or genetic abnormality.

A major portion of the variability in intelligence level is probably genetically determined and a number of genes or polygenes involved in its control. In support of this concept are the large number of different genetic disorders which can cause mental

TABLE 4.—*Heterozygote Detection in Recessive Diseases*

Autosomal Recessive Disease	Heterozygote Manifestations
Acatalasemia	Decreased red cell catalase level
Afibrinogenemia	Reduced fibrinogen levels without symptoms
Crigler-Najjar syndrome	Decreased glucuronide formation with salicylates
Cystic fibrosis of pancreas	Some have increased sweat Na and Cl
Galactosemia	Reduced enzyme activity (galactose - 1 - phosphate uridyl transferase) of red cells
Goitrous cretinism (dehalogenase deficiency)	Decreased dehalogenase activity
Hemoglobin C disease	Hemoglobin C trait (by hemoglobin electrophoresis)
Hypoproconvertinemia (Factor VII deficiency)	Decreased levels of proconvertin (factor VII)
Hypophosphatasia	Reduced serum alkaline phosphatase; excretion of phosphoethanolamine in urine
Non-spherocytic hemolytic anemia (pyruvic kinase deficiency)	Lowered pyruvic kinase activity in red cells
Methemoglobinemia (diaphorase deficiency)	Decreased diaphorase in red cells
Parahemophilia (Factor V deficiency)	Reduced factor V in blood
Phenylketonuria	Abnormal phenylalanine tolerance
Pentosuria	Increased urinary excretion of pentose after glucuronolactone administration
Sickle cell anemia	Sickle cell trait (hemoglobin electrophoresis)
Thalassemia major	Thalassemia minor or trait
X-Linked Disorders	
Hemophilia	Reduced levels of antihemophilic globulin
Muscular dystrophy	Elevated serum creatine phosphokinase
Nephrogenic diabetes insipidus	Reduced ability to concentrate urine
G-6-PD deficiency	Decreased red cell enzyme activity

retardation and the fact that in a population the intelligence test scores tend to fit a unimodal normal distribution. The group that falls on the lower end of the curve will have mental retardation due possibly to an interaction of several genes, none of which alone leads to mental retardation.

In schizophrenia heredity may play a significant, but still undefined role.[32] Siblings of schizophrenic persons have almost a ten-fold increased risk of becoming schizophrenic. In addition, twin studies show a high concordance in monozygous or identical twins. However, there seems to be no familial tendency to a specific type of schizophrenia. Other work suggests that a single gene may be involved if one assumes its action is intermediate between dominance and recessivity. Considerably more work is needed before the role of genetics in mental illness is clarified.

Genetics and Radiation[29]

The increasing exposure to radiation through medical examinations and atmospheric fallout has led to considerable interest in the effect of this radiation on the genetic constitution of man. Although significant experimental work has been done in other species, relatively little direct information is available on the effect of radiation to humans. The natural or spontaneous mutation rate for man has been calculated to be about 10^{-5} (that is, one mutation per locus per 100,000 gametes per generation). The effect of radiation on this rate is unknown. This is because a large proportion of mutations are recessive and only a few may become manifest in the first generation after they are produced. Observations in Japan indicate that one effect of radiation is to cause a reduction in the number of male births (through an unknown mechanism).

Treatment and Management of Genetic Diseases[15]

Genetic diseases cannot be cured. However, this should not cause dismay, since the management and treatment of these disorders is continually improving as more knowledge of them is obtained. Illustrative examples of the various available approaches to different genetic problems are given below.

Elimination diets in phenylketonuria and galactosemia seem to present a successful approach to preventing at least some of the manifestations of the untreated disease. Diseases precipitated by exposure to drugs—such as barbiturates in porphyria or sulfa drugs in G-6-PD deficiency—can be better controlled by keeping the drugs from affected persons. Some hereditary disorders are due to accumulation of substances in the body; the manifestations of hemochromatosis are related to excessive storage of iron in the body, which can be relieved by periodic phlebotomy. In Wilson's disease, copper accumulates is excessive, and removal of it by kelating agents, such as penicillamine, will usually lead to clinical improvement. When a gene product is reduced or missing, such as gamma globulin in agammaglobulinemia or antihemophilic globulin in hemophilia, exogenous replacement of these products improves the symptoms considerably. Exchange transfusions are an important part of management in erythroblastosis. A possible future extension of replacement therapy may be through tissue or organ transplantation—for example, bone marrow replacement in hemoglobinopathic conditions. Colectomy in premalignant cases of polyposis of the colon is a good example of preventive medicine. Surgical operation can also play a role in controlling the manifestations of genetic disease, such as splenectomy in hereditary spherocytosis.

Genetic Counseling[10,15,28]

Genetic counseling is probably the most unique aspect of clinical medical genetics. However, all physicians become involved with problems requiring knowledge in this matter.

Good genetic counseling includes a diagnosis and a prognosis. This will concern the affected person, relatives and persons yet unborn. Ideal prerequisites for good genetic counseling include: A clearly established diagnosis; a careful and complete family pedigree, and examination of additional family members when possible; a background in basic genetic principles; and knowledge of the recent literature concerned with the disease in question. Common sense, good judgment, compassion and awareness of social stigma which may sometimes be associated with genetic diseases are important in counseling.

There is general agreement that it is best to give the facts and let the family members make their own decision, for example, as to whether they should have more children. The manner in which counseling is given may make more of an impression than the facts themselves, and it should be obvious that different people may look on a certain risk differently, depending in part on what they expected the recurrent risk to be. For example, if one anticipates a 100 per cent risk, a 25 per cent risk may seem reasonably favorable.

Knowledge of recurrence risks assumes a major role when one is concerned with the possibility of unborn persons being affected with an hereditary disorder. When the disease in question is due to a specific genetic factor and the inheritance pattern for the disease has been established, it is possible to give definite statistical risks or recurrence risks

based on the laws of inheritance for autosomal dominant, autosomal recessive and sex-linked traits. (These were discussed previously under *Types of Inheritance*, and were also shown in Table 1.) It should be emphasized that only statistical chances can be given and that one cannot predict the outcome of a given pregnancy.

For many diseases a familial pattern may seem to be present, but the pattern of inheritance is not simple or established. In these situations empiric risk figures are available, based on the study of large numbers of cases. In general it seems that the more common a disease, the more difficult it is to provide accurate and helpful risk rates for genetic counseling.

Presentation and discussion of some of these recurrence risk figures may be of value. In occasional families there may seem to be an unusual tendency for a specific defect to occur; these families have to be considered separately and general empiric risk figures should not be used. Congenital diseases often present occasions for giving recurrence risk figures to parents. Table 5 summarizes data for anencephaly and spina bifida aperta, and hare-lip and cleft palate.[7,8]

Clubfoot occurs about once in 1,000 births and usually no simple pattern of inheritance is apparent. If neither parent is affected, but there is one affected child, the recurrence risk in future pregnancies is 3 per cent. If the parents are close relatives this figure can be 3 to 25 per cent.

Congenital heart disease, not associated with specific syndromes, has almost a 2 per cent chance of recurrence in a family of normal parents and one affected child.[7]

About 6 per cent of the population is at risk to develop diabetes by age 80. However, if unaffected parents have a diabetic child, a subsequent child has a 5 per cent chance of becoming diabetic before age 20 and a 10 per cent chance of becoming diabetic by age 60. A child of an affected parent has a 5 to 15 per cent chance of becoming diabetic by age 30.[7]

Epilepsy has a 0.5 per cent incidence in the population. It has been noted that 3.2 per cent of parents, siblings and children of epileptics are epileptic. However, 22 per cent of the siblings of children having "centrencephalic" epilepsy, also gave a history of seizures varying from only one or two seizures to a chronic medical problem of seizures.[7]

Siblings of a child with nonspecific severe mental deficiency have a 3 per cent risk of also being mentally retarded.[7]

Chromosome anomalies present a special group; and mongolism, which has been the most extensively studied,[23,26] will be discussed here.

The recurrence risks are considerably different in the common trisomy 21 and the less common translocation varieties. At this time the only way to distinguish these two groups is by chromosome analysis. The recurrence risk for the translocation type depends on the type of translocation and is considerably higher than for trisomic mongolism. If the translocation occurs between a chromosome 21 and chromosome 22 or one in the D group (13-15), the theoretical distribution among the siblings of an affected person is an equal proportion of translocation mongols, normal individuals and normal carriers of the translocation. Hence the recurrence risk is 33 per cent. If the translocation occurs between two chromosomes 21, all surviving siblings will also be translocation mongols, giving a recurrence risk of 100 per cent.

Translocation mongols form part of a group which seems to be maternal age independent—that is, the maternal age does not affect the frequency.

About 80 per cent of the mongols form a group in which incidence increases with maternal age and who have the usual trisomy 21 chromosome abnormality. In general the incidence of mongolism is

TABLE 5.—*Recurrence Risk Figures (Adapted from Fraser[7,8])*

Disease	*One Child Affected*	*Two Children Affected*	*Per Cent Risk for Anencephaly*	*Per Cent Risk for Spina Bifida Aperta*
Anencephaly	X	....	1	2
	....	X	10	10
Spina Bifida Aperta	X	....	1	2
	....	X	10	10

Disease	*Normal Parents*	*One Affected Parent*	*One Affected Child*	*Two Affected Children*	*Per Cent Recurrence Risk*
Hare-lip with or without cleft palate	X	....	X	....	4-7
	X	....	....	X	10
	....	X	....	....	2
	....	X	X	....	11
Cleft palate without hare-lip	X	....	X	....	2-5
	....	X	....	....	7
	....	X	X	....	17

TABLE 6.—*Recurrence Risks for Trisomic Mongolism at Different Maternal Ages (Adapted from Carter and Evans[2])*

Maternal Age	*Per Cent Recurrence Risk (Approximate)*
15-19	0.05
20-24	0.1
25-29	0.1
30-34	0.15
35-39	0.4
40-44	1.1
45 plus	1.9

TABLE 7.—*Genetic Identity Between Relatives*[30]

Relation	*Proportion of Genes in Common*
Identical twin	1
Parent, child, sibling, fraternal twin	1:2
Grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling, double first cousin	1:4
First cousin	1:8
First cousin, once removed	1:16
Second cousin	1:32
Third cousin	1:128

TABLE 8.—*Proportion of Consanguineous Marriages in Some Autosomal Recessive Diseases*[13]

Disease	*Frequency of Homozygotes*	*Frequency of Heterozygotes*	*Per Cent in Consanguineous Marriage*
Cystic Fibrosis of Pancreas	0.0009	0.06	No increase
Adrenogenital Syndrome	0.0002	0.028	No increase
Tay-Sachs disease	0.00012	0.022	2
Albinism	0.00005	0.014	8
Phenylketonuria	0.000035	0.012	10-12.5
Cystinosis	0.000025	0.01	12
Hurler syndrome	very rare	....	20-30

TABLE 9.—*Genetic Counseling Centers in California*

Location	*Person to Contact*
1. Children's Hospital, Los Angeles	Dr. George Donnell
2. Children's Hospital, San Francisco	Dr. David Linder
3. City of Hope Medical Center, Duarte	Dr. William Kaplan
4. Department of Medicine, County General Hospital, Los Angeles	Dr. Russell Rohde
5. Department of Biology, San Diego State College, San Diego	Dr. Kenneth Taylor
6. Department of Medicine, Stanford Medical Center, Palo Alto	Dr. Thomas Merigan
7. Department of Pediatrics, University of California Hospital, San Francisco	Dr. Carolyn Piel
8. UCLA Medical Center, Los Angeles	Dr. Stanley Wright (Department of Pediatrics) Dr. Robert Sparkes (Department of Medicine)

about one in 600 births. However, depending on the age of the mother the risk may vary from about one in 2,500 in young mothers to one in 50 in old mothers. The incidence for various age groups is summarized in Table 6. Taking all mongols as a group: the overall chance of recurrence regardless of maternal age is 1 to 2 per cent; if the mother is under 25 years of age the recurrence risk is 50 times the random risk for her age group. This decreases to five times the random risk for mothers aged 25 to 35. There is no increased risk for mothers over 35. If the parents are normal, the mother is under age 35 and the affected child has trisomy 21, the recurrence risk is six times the random risk for the mother's age.

The recurrence risk for other chromosome anomalies is less clear. Theoretically it may be somewhat similar to that for mongolism, depending on the general incidence of the anomalies. A maternal age effect also seems to be present for the D_1 and E trisomies as well as the Klinefelter syndrome.

Consanguinity[17,31]

Consanguineous marriages or marriages between close blood relatives are limited in our society. When considering recessive diseases, avoiding such marriages is a sound genetic policy, because random mating is less likely to bring two rare recessive genes together than if blood relatives marry. Table 7 shows the proportion of genes in common between relatives; it is generally thought that marriages between individuals less closely related than second cousins have little practical chance of increasing the risk of occurrence of recessive diseases in their offspring. Table 8 shows the importance of consanguineous marriages to the frequencies of some diseases.

The chance that a person with a recessive disease will have a similarly affected child is low, but marriage to a first cousin causes a 64-fold increase in the risk.

Sources of Genetic Counseling in California

Physicians are often hesitant to become involved in genetic counseling. The above discussion only touches on some aspects of medical genetics and genetic counseling. Therefore, a list of people and institutions in California known to the author to be interested in genetic counseling is presented herewith (Table 9).

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